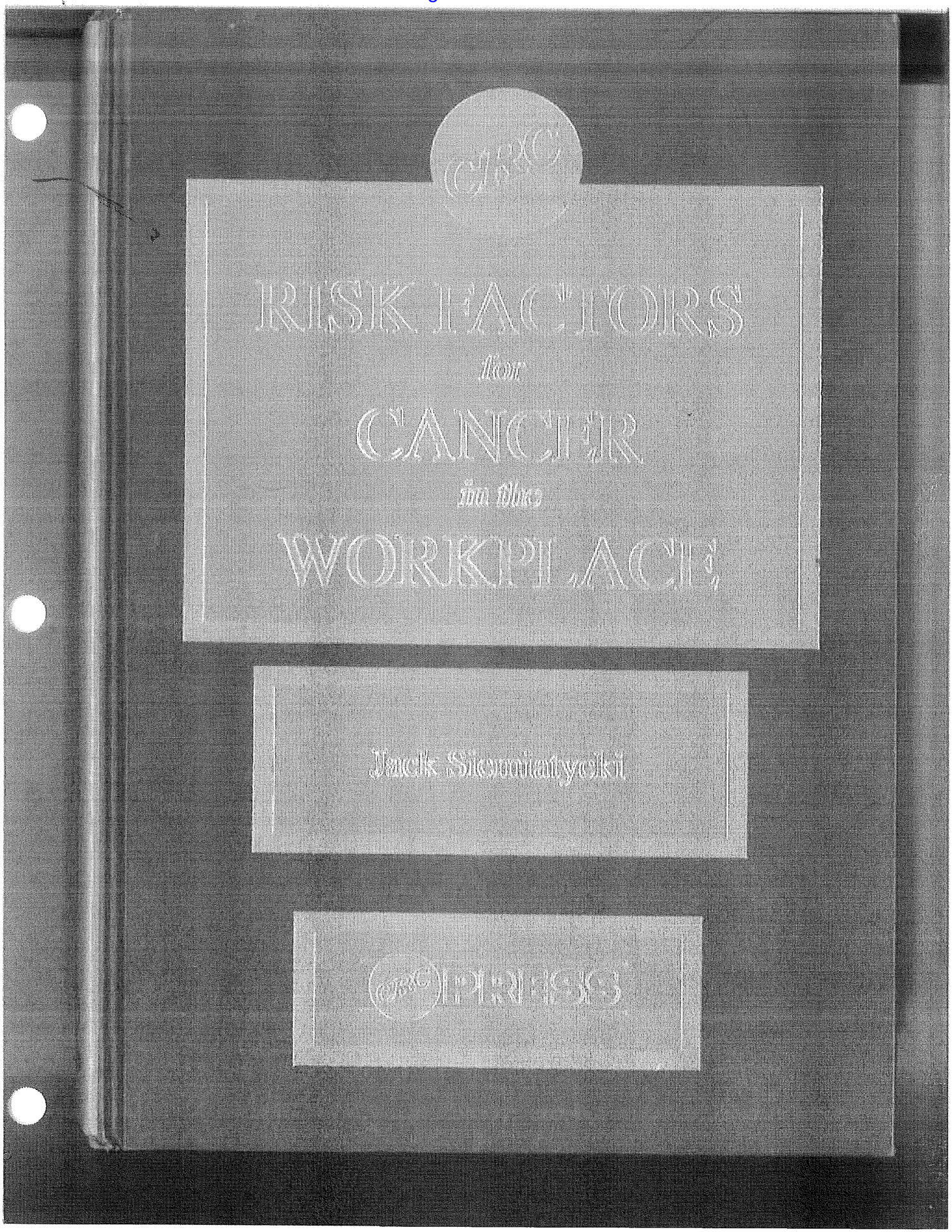
Exhibit 27


RISK FACTORS
for
CANCER
in the
WORKPLACE
Jack Siemiatycki

Chapter 7

IN P ION OF FINDINGS

Jack Siemiatycki

BL OF CON N S

I. INTRODUCTION

The main purpose of epidemiology is to find the cause of disease. Despite some controversy concerning the validity of drawing causal inferences in epidemiology,[1-4] there is a consensus that sanctions and provides guidelines for the practice. The evaluation of causality between a putative risk factor and a disease is a complex and subjective process. Equally competent scientists, examining the same information, can arrive at different conclusions. However, as additional evidence is accumulated, beliefs and consensuses may change.

The criteria that are most relevant to the problem of evaluating causality between cancer and an antecedent occupational exposure may be paraphrased as follows: (1) Is sampling variability a plausible explanation for the observed association? (2) How strong is the association, and is there a dose-response relationship? (3) Is bias or confounding a plausible explanation for the observed association? (4) Is the association biologically plausible? (5) Is there relevant supporting evidence from other epidemiologic studies or from nonhuman test systems, such as animal experimentation or tests of mutagenicity?

In Chapter 6, we presented evidence on tens of thousands of associations. To evaluate the causal inferences that can be drawn in regard to every association would be beyond the available means. Not only would it be necessary to conduct more detailed and focused statistical analyses on each association, but it would be necessary to conduct exhaustive literature reviews concerning each association. Although such work is beyond the scope of this volume, there are some general comments that can help the reader to interpret and use the results shown in Chapter 6, as well as other similar sets of results.

II. SAMPLING VARIABILITY

There are several pertinent aspects to the issue of sampling variability: statistical power to detect risks, false positive results due to multiple testing, and the interpretation of individual results. Given the relatively low prevalence of exposure of most occupational exposures and the numbers of cases that could be assembled for this study, the statistical power to detect risks was limited. For many, perhaps most, associations studied, the statistical power was so low that only very large relative risks could have been detected. The wide confidence intervals around most odds ratios illustrate the low resolution of these results. Low statistical power was a major cause of false null results in our study. This problem could be remedied in theory by increasing the sample sizes of case and control groups, which would be achieved either by extending the duration of the study or by enlarging its geographic catchment area.

In a study which includes multiple hypotheses, there will inevitably be false positive (as well as false negative) results. Although it is sometimes assumed that these false positives are merely statistical artifacts on paper, they do in fact represent coincidences that occur in the real world, irrespective of whether or not epidemiologists are there to observe them and irrespective of whether it is observed as part of a multi-variable monitoring system, such as ours, or a single factor study or a case report by an astute clinician. It is noteworthy that each result observed in our study would have been the same had the project been undertaken to study only that association. For instance, the association between abrasive dust and gallbladder cancer seen in Table 2 in Chapter 6 with an OR of 3.1 (90%CI: 1.5 - 6.1) would have been exactly replicated had we carried out a case-control study of gallbladder cancer using other cancers as controls and focusing only on abrasive dust as a possible risk factor, evaluated in the way we evaluated exposures. One of the benefits of a systematic data collection system is the ability to place the observed associations into an overall probabilistic context.

As shown in Table 8 in Chapter 6, for most sites of cancer examined, the numbers of significant results observed did not exceed the numbers expected. The prominent exception was lung cancer for which there was a considerable excess of observed over expected. For

lung cancer, these data are compatible with the hypothesis that there are several true positive associations among those which appear to be positive associations. For other sites, these data are compatible with the hypothesis that there are no true positive associations. However, the statistical variabilty of these estimates is such that a small number of true positives is almost as likely as none. For instance, if there were two true associations in our data set for colon cancer, then the expected number of significant positive associations would be 52.3 rather than 50.3. The observed number, 51, is hardly more compatible with one than with the other. Thus, we may conclude that for colon cancer, as for most sites evaluated, the results are compatible with the presence of no or few true associations. But in scientific and public health terms, the discovery of a few new colon carcinogens would be of tremendous importance. There was a striking deficit of observed compared with expected significant results for skin melanoma. It is possible that this is a reflection of some uncontrolled confounding. Otherwise, it indicates that melanoma patients were disproportionately represented among occupations with few exposures coded. The hypothesis of an excess risk of melanoma for white-collar workers is compatible with the hypothesis of an excess risk due to fluorescent lighting in office buildings, an exposure which was not included in our exposure assessment.

In evaluating the evidence concerning a specific association, the multiple inference context is irrelevant. The reader interested in a particular association which we have reported should interpret our result as (s)he would if the study had been conducted only for that association. The confidence interval is useful in assessing the plausibility of the null hypothesis. The higher the lower confidence limit, the less likely it is that the elevated odds ratio is an artifact of sampling variability.

S RE G H OF ASSOCIA IO A D DOSE-RESPO SE

The size of an odds ratio is an important consideration in evaluating the plausibility of a causal relation. For a given level of statistical significance, the larger the OR the less likely it is that the result is an artifact due to confounding.

The information provided in the various results tables in Chapter 6 includes the estimates of odds ratios at two levels of exposure, one embedded within another. These levels of exposure, any and substantial, are not defined according to absolute or precise measures of exposure. If a substance is carcinogenic, the dose-response relationship can take many forms, but for most known carcinogens the curve is monotonic. As a general rule, an association which displays a greater OR at the substantial than at the any exposure level is more impressive than one which does not. Nevertheless, it is possible that the shape of the curve is quite flat in the range of exposure levels in our population, in which case we might observe an excess risk but no difference between the two exposure levels. While the comparison of OR estimates between the two exposure levels is recommended in assessing the plausibility of the evidence, the usefulness of this comparison is limited in our study by the wide and usually overlapping confidence intervals. More refined analyses can and will be carried out to assess the effects of duration, concentration, frequency, and latency on disease risk. These analyses should be tailored to the association being studied.

IV. BIO OGIC P A SIBI I Y

It would seem that information o absorption, kinetics, metabolism, and excretion of a substance would be valuable in assessing its possible effect on a given body organ. One apparently straightforward issue is whether the substance or its metabolites ever reach the target organ. For instance, there clearly is contact between respirable dusts and the respiratory tract. However, the fate of foreign chemicals and their metabolites in the body is so complex and our knowledge in this regard so limited that it is often difficult to ascertain whether a given

substance or its metabolite contacts a given target organ.[5] In general, biologic plausibility is a rather poorly defined and elusive concept. It is elusive because our understanding of biological processes is imperfect and evolving, and what may seem implausible at one time may seem plausible later on, as is illustrated by the association between smoking and cervical cancer.[6]

Among currently recognized associations between occupational exposures and cancer (Tables 1 and 2 in Chapter 1), certain target organs appear more frequently and some do not appear at all. There has been some tendency to consider that a target organ which has been demonstrated in the past to be associated with an occupational exposure is more liable to be associated with another substance than a target organ which has not been so demonstrated.[7] However, this assumes that past methods for discovering associations have been effective, a dubious assumption. The absence of previous associations with a given site should not be considered persuasive evidence against that site being a potential target organ for carcinogens.

V. BIAS AND CONFOUNDING

A. COMPARABILITY OF BASE POPULATIONS FOR CASE AND CONTROL SERIES

For each case series studied, the cases represented a well-defined, virtually exhaustive group of eligible cancer patients in the Montreal area. Two control groups were used, a sample of patients with other types of cancer and a population control series. Since the cancer controls represented a sample from the same population-based ascertainment as the cases, they satisfy the requirement that they represent those people in the base population who would have been in the case series had they had the cancer of interest. The population control series was selected from electoral lists and by random digit dialing and is thought to also satisfy this criterion.

B. NONRESPONSE BIAS

Not all subjects selected for study agreed to be interviewed. Response rates ranged from 78 to 85% for most cancer sites and was 75% for the population controls. In itself, lack of participation does not cause bias, but different response rates in the four subgroups (exposed cases, exposed controls, nonexposed cases, nonexposed controls), may lead to a distorted picture of the association.[8] The opportunity for such bias is greater if the response rate is low. Because of the relatively low response rate among population controls, the comparison of cancer cases with population controls provides greater opportunity for nonresponse bias than the comparison with cancer controls. The opportunity for bias is realized when different types of people have different response rates according to whether they are cases or controls. This is unlikely to occur between cancer groups; therefore, the risk of bias is minimal for the cancer control comparisons. It is more plausible that the types of people who do not respond in a population control group differ from the types of people who do not respond among cancer patients; thus, there is some likelihood of bias in the population control comparisons. Such bias could operate in either direction, either exaggerating or attenuating risk estimates.

C. INFORMATION BIAS

It is also important that the information collected and used in analyses be of equivalent quality between cases and control series. The production of information can be viewed as having occurred in two stages. The first stage was the interview, and the most important part thereof was the detailed job history. The quality of interview response certainly varies from one subject to another depending on the memory and motivation of the respondent, the skill of the interviewer, and the environment and ambiance in which the interview is conducted. It is conceivable that the quality of response differs on average between cancer patients and healthy subjects. The cancer patient is more motivated to collaborate and is less likely than

a healthy subject to view the interview as an unwelcome intrusion into his normal routine. On these grounds we would expect a greater degree of accuracy in recalling and reporting occupational exposures among cancer cases than among population controls. Furthermore, it was impossible to blind the interviewers to the difference between cancer cases and healthy controls, and their prior beliefs about what they might hear may also have colored the resulting interview. However, there should be no such biases operating between cancer cases and cancer controls. The degree of anxiety and motivation would be similar on the part of different cancer patients. Also, the interviewers, who in general were not aware of what type of cancer the patient had, would be unlikely to systematically interact differently with patients having different types of cancer.

The second step in data collection was the translation of job histories into exposure histories by the team of chemists and hygienists. This activity, which served to distill and homogenize the information collected in the first step, was done without the chemists and hygienists' having access to information concerning the subject's disease status. As a result, the codings were of comparable quality between the different case and corresponding control groups.

D. CONFOUNDING BY NONOCCUPATIONAL VARIABLES

As shown in Table 5 in Chapter 3, the various study groups were not identical on important covariables. There were some differences among the various groups in age, ethnic origin, and other factors, and this would lead to inequalities between case and control groups. Some of these differences result from the associations between these variables and the different cancer sites and some are just the result of statistical fluctuation.

The main approach to controlling confounding was to include variables in the Mantel-Haenszel analyses as stratification variables. For each site, we identified those variables which were potential confounders and which we had available to us (Tables 2 and 3 in Chapter 5). There still remains a chance of confounding due to variables that we did not collect and which are risk factors for cancer. There is also the possibility that the statistical form of controlling by means of the Mantel-Haenszel stratification is incomplete and leaves residual confounding. Several authors have shown that confounding due to nonoccupational variables is unlikely to distort an OR between cancer and an occupation group by more than 40%.[9] That is, an OR of 1.4 or greater between an occupational title and cancer is unlikely to be an artifact due to confounding by nonoccupational variables.

The correlation between cancer risk factors, such as smoking and social class, and occupational variables is likely to be much higher when the occupational variable is an occupational or industrial title than when it is a specific substance. That is, personal characteristics may well be related to the occupation or industry in which a man finds himself, but they would only be correlated with substances indirectly, by virtue of their correlation with occupations and industries. Thus, the likelihood of confounding by nonoccupational variables is probably even less for associations with specific substances than it is for associations with occupation or industry titles.

One of the strongest nonoccupational risk factors for many sites of cancer was ethnic group, presumably because that variable embodies both genetic and socio-cultural differences. One tactic used to mitigate the possibility of confounding due to ethnic group was to carry out a whole set of analyses among French Canadians only. This served to pick up risks that were masked in the analysis of all ethnic groups combined.

E. CONFOUNDING BY OCCUPATIONAL EXPOSURE

A much more important problem is the fact that the association between cancer and one occupational substance may be confounded by other occupational substances. This is a greater potential problem because occupational substances tend to cluster in workplaces, producing very high correlations and an opportunity for confounding. If one substance is a true carcino-

gen, then it is quite possible that some other substances with which it is highly correlated would also appear to be associated with cancer. For this book we have not carried out the analyses that would be needed to try to tease out which of the ostensible risk factors is the carcinogen and which are associated by virtue of their correlation with the prime agent. Such analyses would have to be tailored to each situation. For now we can provide some general guidance. If a substance is associated with a given cancer site, then the reader can ascertain, in Table 1 in Chapter 4, the list of substances with which it is strongly correlated. A first impression as to the possibility of these co-exposures confounding the index association is provided by the associations between those highly correlated co-exposures and that type of cancer, as shown in Table 7 in Chapter 6. If no co-exposures show an association with the same site, then it is unlikely that there is substantial confounding. If multiple correlated co-exposures are associated with the same type of cancer, the effect may be due to one of them or to several of them. Even this informal approach to assessing possible confounding by occupational variables may fail if the true causal agent is an occupational exposure which was not coded validly by our team of chemists or which was not even on the checklist of exposures to evaluate.

F. MISCLASSIFICATION OF CASE OR CONTROL STATUS

There would be a problem if the case group included people who did not really have the disease or if the control group included people who did. There is a national health insurance system in Quebec and a well-developed medical infrastructure in the study area which ensures uniform high quality diagnostic services to the population. The requirement for histopathologic confirmation of cancer among cases provides considerable confidence that each case series was really composed of cases of the respective type of cancer. However, there was no special clinical or histopathological review of diagnoses for this project and there undoubtedly is some degree of error in cancer diagnosis, especially in the designation of histologic subtypes.[12] For each cancer case series, given its low prevalence in the population, it is unlikely that any of the population controls had the type of cancer being analyzed. The chance of misclassification was slightly higher when using cancer controls because of possible misdiagnoses of metastatic tumors. Misclassification of case or control status was probably a minor source of bias, except possibly for the histologic subtypes of lung cancer. The effect of any misclassification of disease status would have been to attenuate risk estimates.

G. MISCLASSIFICATION OF EXPOSURE

Probably the most serious source of bias in this study is that due to misclassification of exposure status. The procedures developed and implemented over the 10 years of data collection represent one of the most intensive efforts yet to retrospectively assign exposures in a population-based study. Considerable time and resources were invested. Despite the lack of hard evidence, we believe that the assessments made about the historic exposures of study subjects, as described in Chapter 4, were reasonably correlated with the truth. Nevertheless, there was undoubtedly some degree of error in the process. This error was mainly nondifferential with respect to case or control status of subjects, although there may have been a slight tendency for better quality of interview data from cancer patients than from population controls.

Whatever nondifferential misclassification there was would have had the following effects. For true null associations, the random misclassification would not be expected to change the OR estimate. For true positive associations, however, it would have the effect of attenuating the true OR towards the null value of 1.0. The degree of attenuation would be proportional to the degree of misclassification. It is important to note that this type of misclassification would not spuriously create associations where there are none. Thus, the appearance of an association cannot be attributed to nondifferential exposure misclassification. On the contrary, the ob-

served effect may well be a pale reflection of the true, much larger OR. A null finding, on the other hand, may be due to a misclassification error.

VI. SUPPOR FROM O H R SOURC S

Evidence from a single epidemiologic study is rarely, if ever, sufficient to incriminate a substance as a causal factor. There are too many sources of potential bias and confounding in any single epidemiologic study to allow confidence in making causal inferences. Because epidemiologic studies, unlike laboratory experiments, tend to occur in unique and distinct circumstances, the possible sources of bias and confounding are usually different from one study to another, even when the studies purport to concern the same hypothesis. When the same result is found in several studies, each with its distinct baggage of potential sources of bias, it becomes more reasonable to take that common result at face value. The second benefit of replication is to further reduce the probability that the observed result was a fluke due to sampling variability.

However, although consistency of findings across studies is an important criterion for judging causality, it is a criterion that can serve to mask true excess risks in particular circumstances. Cancer risk is a function of the degree of exposure and concomitant circumstances. It is quite plausible that workers exposed to a carcinogen in one study population experienced much lower exposure levels than workers exposed to the same substance in another study, and that these differences create high risk in one place and little or no risk in the other. Since absolute exposure levels are rarely available for the etiologically relevant era, it is difficult to ascertain whether an apparent discrepancy of findings can be explained on the basis of differing exposure levels. In a similar vein, many carcinogenic circumstances are identified not by a specific chemical, but by a class of chemicals (e.g., nickel compounds), or by a mixture of variable composition (e.g., soot). For such substances, it is possible that exposure to one form of such a class or mixture is carcinogenic while others are not. Not only is the risk a function of the qualitative and quantitative nature of exposure to the putative carcinogen, but because cancer is a multifactorial disease it is also a function of the host of concomitant circumstances, such as other occupational exposures and the nonoccupational characteristics of the workers involved. It is possible that at the same level of exposure to a given carcinogen one group of workers would experience high ORs and another group would experience low or even null ORs. These considerations preclude the use of consistency of findings as a criterion to be applied mechanically; rather, the review of different studies requires considerable subtlety.

While the most directly relevant supporting evidence comes from other epidemiologic studies, meaningful supporting evidence can come from animal experiments or even from so-called short-term tests of potential carcinogenic activity.

For many of the thousands of associations for which we have presented results, there are other studies, either epidemiologic or experimental, which can shed light on the validity of our findings. It is unrealistic in the context of this book to undertake the exhaustive literature reviews that would be required for each of these associations. Yet, without such reviews it is impossible to try to draw inferences from our findings. Consequently, we have deliberately restricted our task to the presentation of results rather than their interpretation. For many of the associations which we present, there is no other literature and our result is the only one available.

VII. H PO H SIS S ING AND H PO H SIS G N RA ION

There is a common misconception that a result should be interpreted differently if it comes from a so-called hypothesis-generating study or a hypothesis-testing study. What counts is the

way this piece of evidence fits into the total evidence on a hypothesis. Because the piece of evidence from a hypothesis-generating study is often the only evidence available on the topic, one should be circumspect about drawing conclusions. On the other hand, because the piece of evidence from a hypothesis-testing study is often supported by previous evidence which was in fact the motivation for the study, one can usually interpret the results with more assurance. But it is the context of confirmatory evidence rather than the motivation of the investigator that may justify different inferences. If a finding from our study is supported by other evidence, it would merit the same weight as if the study had been conducted to test that hypothesis.

V . H US OF H S R SUL S

This set of results can be used for two purposes: to evaluate specific associations and to set priorities for future research. Associations were evaluated between the 23 cancer groupings shown in Table 1 in Chapter 5 on the one hand and the 293 substances (listed in Table 1 in Chapter 4), 98 occupation groups (listed in Appendix 1 in Chapter 5), and 77 industry groups (listed in Appendix 2 in Chapter 5) on the other. Because of the large volume of results produced, only a fraction were presented. If any association of interest to the reader is not shown explicitly in any of the tables in Chapter 6, the inference can be drawn that there was low statistical power to detect a risk and the result was compatible with the null hypothesis. In general, the confidence interval for such associations would be very wide, and it would not be possible to rule out a sizeable risk. The interested reader can obtain, upon request from the authors, any specific results not found in these tables or a diskette with the whole mass of results.

For a result which is shown and which is null, there are a few possible interpretations, besides the obvious and most probable one that there really is no association. Exposure misclassification for that substance may have been so severe as to attenuate the OR estimate towards the null. In a slightly different vein, it may be that there is a true association at high levels of exposure to the substance, but that the levels at which most workers in our study population were exposed were too low to induce any detectable risk. Sampling variability can play a role in masking true associations, just as it can in creating false positive associations. The confidence intervals around ostensibly null ORs usually include values above 1.0, and because of the modest statistical power available even for the main sites, the upper confidence limits were rarely less than 1.3. For rare sites or rare exposures, the upper confidence limits were rarely less than 2.0.

For apparent positive associations, the main possible explanations, besides the presence of a true causal association, would be sampling variability and confounding by other occupational exposures. The fact that we estimated eight odds ratios for each association, with the purpose of maximizing the sensitivity to detect hazards, certainly increased the opportunity for sampling variability to induce false positive associations. The inability to formally rule out mutual confounding by occupational exposures is a drawback, but it does not compromise the primary objective of detecting that there is a real problem that requires explanation. If an association was observed and if statistical variability and confounding due to nonoccupational sources are thought be unlikely, then it is justifiable to infer that an occupational hazard of some sort has been uncovered, even if the substance ostensibly at fault may be manifesting the true effects of another. The first step in discovering a carcinogen is the realization that there is an excess risk that requires an explanation.

X. EVALUAT NG SPE F ASSO AT ONS

It is interesting to note our findings concerning selected associations which have either

been well established or suspect.[3,4] Chrysotile asbestos was clearly associated with lung cancer (OR: 1.5; 90% CI: 1.1-1.7) and with mesothelioma (OR: 4.4; 90% CI: 1.6-11.9). The lung cancer association held for all histologic types examined. Chrysotile asbestos did not display any pattern of excess risk for gastrointestinal or other sites. Amphibole asbestos was less prevalent than chrysotile and, consequently, provided lower power to detect risks. Only mesothelioma was at risk, with a risk estimate higher than that for chrysotile (OR: 7.2; 90%CI: 2.6-19.9). There was considerable opportunity for confounding among these two substances; four cases of mesothelioma were exposed to both chrysotile and amphibole fibers and only one was exposed to one but not the other. Glass fiber and mineral wool, often used as replacements for asbestos, were not associated with lung cancer in these data, and neither was industrial talc. Crystalline silica has been touted as a possible lung carcinogen, and our results support this hypothesis (OR: 1.6; 90%CI: 1.1-2.3). The association does not appear to apply to adenocarcinoma of the lung.

PAHs have been incriminated as skin carcinogens and have been suspected as lung carcinogens. In our results, there was some excess risk of lung cancer in relation to PAH derived from combustion of wood, and diesel engine exhaust, which also contains PAHs, but there were no significant associations between lung cancer and any of the following types of PAHs or substances containing PAHs: benzo(a)pyrene, coal tar and pitch, and soot. Several types of mineral oils were evaluated. The only one showing some positive association with lung cancer was "cutting fluids post-1955." The bladder has also been a suspect target organ for cutting fluids, and for this association, we found little supporting evidence.

The suspicion of an excess of lung cancer among welders was supported by our occupation title analyses and by our substance analyses where the category gas welding fumes was associated with lung cancer, albeit with a relatively low OR (OR: 1.2; 90% CI: 1.0-1.5).

Formaldehyde has been a suspect carcinogen for several sites, though the only site for which there is moderately persuasive evidence is the nasal sinus, a site not included in our study. In our data, there is some indication of an excess risk for bladder cancer, but not for lung or any other sites. Also in our data, there was no indication of excess risk in relation to vinyl chloride, acrylonitrile, ethylene oxide, or PCBs, though the numbers exposed in our population to these substances were very small. There was only one case of angiosarcoma of the liver in our study.

We found moderately elevated risks of lung cancer in our data-set for two established classes of lung carcinogens, nickel compounds (OR: 1.4; 90%CI: 1.1-1.9) and hexavalent chromium compounds (OR: 1.4; 90%CI: 1.1-2.0) . Arsenic compounds was a rarer exposure and no elevated risks were demonstrated. Cadmium compounds, which was also a quite rare exposure, did not show excess risks for lung, prostate, or any other cancers.

Although specific aromatic amines were not included in our evaluation, the general class was included and was associated with bladder cancer (OR: 2.1; 90%CI: 0.9-4.6), but the association did not achieve statistical significance.

Some associations highlighted in Table 9 in Chapter 6 distinguished themselves mainly on the strength of the number of cases that would be attributable to the association if it were true. Particularly noteworthy in this regard were the associations between lung cancer and alkanes (C_5-C_{17}), nitrogen oxides, metallic dust, aluminum compounds, and those between squamous cell lung cancer and PAHs from petroleum, PAHs from any source, and solvents. For those associations the odds ratios were rather low, in the range of 1.3 to 1.4, and confounding effects could have produced the apparent effects. Some associations were distinguished by exceptionally low p values, but tended to be based on rather small numbers of cases, e.g., stomach and zinc dust, small intestine and cooking fumes, mesothelioma and insulation dust, adenocarcinoma of the lung and antimony compounds, kidney and both felt dust and jet fuel.

Table 10 in Chapter 6 highlights the most promising associations which had odds ratios below 1.0 and which could reflect some protective or anticarcinogenic effects. Liver cancer

cases showed a noteworthy deficit of exposure to several substances, many of which are components or correlates of engine emissions.

For all these associations, as well as for many others, we will be carrying out additional statistical analyses. In-depth analyses will be based on logistic regression models and will include for each association a number of potential occupational and nonoccupational confounders identified empirically within our data set by a method we have used previously.[15 16] In-depth analyses will also examine more closely the risk as a function of various available indices of exposure, namely the concentration, frequency, duration, and era of exposure as well as the confidence with which exposure was attributed. The effects of the exposure will be assessed in different occupations or industries in which it occurs, and for the more common exposures, interaction effects will be estimated.

X. EVALUATION O THIS METHOD O DISCOVERIN CARCINO ENS

In 1979 we undertook a novel approach to discovering occupational carcinogens. If the design is sound, the data collection methods valid and the statistical methods appropriate, then we have reason to expect the results to be valid. The design is based on fairly standard principles of case-control studies, though the multiple cancer group nature of the comparisons is somewhat unorthodox. Except for those occupational exposures which cause cancer at multiple sites, classic theory tells us that our design is sound. The statistical analysis methods used are fairly standard, although for the purpose of this volume we have not undertaken the difficult task of trying to control for the mutual confounding effects of the different occupational exposures. The data collection methods, especially the evaluation of historic exposures, were novel and difficult to validate. A major problem was the low statistical power due to relatively low sample sizes, but given sufficient time and resources, this problem can be remedied.

One traditional approach to generating hypotheses has been to wait for astute physicians to observe and report case clusters. This is inadequate. The traditional epidemiologic approach to monitoring the entire industrial spectrum has been based on the analysis of job or industry titles, either obtained from routine records or by interview. There is little doubt that our in-depth evaluation of job exposures produces higher quality and more relevant data than just job or industry titles.

Perhaps the validity of our approach should be assessed by its success in detecting risks which are well known, such as those listed as definite in Table 1 in Chapter 1. Unfortunately, most of those associations cannot be evaluated in our data-set, either because the substance was not part of our exposure checklist (viz., 2-naphthylamine; 4-aminobiphenol; benzidine; BCME; radon; talc containing asbestiform fibers) or because the type of cancer affected was not included in our study (viz., nasal cancer; nonmelanoma skin cancer; leukemia). While angiosarcoma of the liver was included in principle, it was not in practice since there was only one incident case in the period of the study; only 5 associations listed as definitely established in Table 1 in Chapter 1 were addressed in our study. A sixth one, aromatic amines and bladder cancer, is implicit in Table 1 in Chapter 1 since 3 specific members of this class (viz., 2-naphthylamine, 4-aminobiphenol, benzidine) are listed in the table. For two of the six associations (asbestos and lung cancer; asbestos and mesothelioma), our results were clearly significant. For three others (hexavalent chromium compounds and lung cancer; nickel compounds and lung cancer; aromatic amines and bladder cancer), our results indicated elevated risks, though the tests were not consistently significant. For the association between arsenic compounds and lung cancer, we found no evidence of excess risk. As mentioned above, because of qualitative and quantitative differences in the exposure and co-exposure circumstances from study to study, it would not be surprising to find no detectable risk in our

population-based case-control study for an association which was previously demonstrated in a highly exposed cohort. In aggregate, these six comparisons show a rather encouraging degree of agreement.

However, the real test of our method will be the test of time. In the long run, it will become apparent whether or not this body of results has provided risk estimates that are borne out as valid.

X . F T RE D RECT ON

Epidemiology is increasingly and appropriately being called upon to provide information on disease risk factors. In the past, the main efforts went into fixed-length studies focused on specific hypotheses, with some marginal effort devoted to broadly based monitoring-type studies. While the former were often successful, the latter rarely were. The magnitude of the problem of assessing the impact of innumerable potential risk factors on many diseases demands more efficient approaches to producing evidence. The population-based case-control approach is an efficient approach that can be used to study in some depth many potential risk factors. In the area of occupational cancer, we believe this is an approach that could and should be implemented widely. It should be ongoing and would thereby derive the statistical power to provide reasonably precise risk estimates and the capacity to detect new hazards as soon as their effects become manifest. Many other areas of concern, such as cancer and diet, or reproductive outcomes and occupation, would also be amenable to and would greatly benefit from the implementation of analogous approaches. Trying too hard to fit into the mold of other biomedical sciences, epidemiology has been too intent on carrying out short-term, narrowly focused studies and not sufficiently bold about long-term, broadly focused studies.[17] The latter have often been deprecated as being in the province of routine government data collection as opposed to the more academic and demanding work of evaluating specific hypotheses. We hope that our work demonstrates this to be a false dichotomy. Long-term, broadly based case-control studies are at least as methodologically sophisticated as short-term, narrowly based ones and they can produce data of high quality. They deserve an important place in the corpus of epidemiologic activity. The necessary moves in this direction are partly impeded by anachronistic attitudes to broadly based studies within the discipline and partly by the structural difficulties of financing and conducting them. But, as these attitudes and barriers are overcome, such studies may come to play a dominant role in biomedical research in the 21st century.

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